> If the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to distinct and/or independent inventions.

As stated in the Response to Restriction Requirement filed July 27, 1998, the restriction requirement is improper because the Examiner has not shown that a search and examination of the entire application, in particular, Groups I and II, would indeed cause a serious burden, as required by MPEP §803 for proper restriction. In fact, a serious burden would arise only if examination of the patent application were restricted to one of the claim groups. Filing additional patent applications containing the non-elected claims would unnecessarily burden (1) the U.S. Patent and Trademark Office (USPTO), since it must assume the additional labor involved in examining at least two separate applications; (2) the public, since it will have to analyze at least two patents (assuming the subject matter of each claim group is found patentable) to ascertain all of the claimed subject matter; and (3) the Applicants, since the Applicants must bear the substantial financial burden and delays associated with the prosecution of multiple patent applications and the payment of maintenance fees for multiple patents.

It is submitted that any additional burden on the Examiner in considering, in particular, Groups I and II together is not so serious as to require restriction, especially in view of the fact that the Examiner has already issued a substantive Office Action (mailed September 7, 1997) directed to these two groups. Therefore, Applicants respectfully request withdrawal of the restriction requirement as between the claims of Groups I and II.

Should the Examiner maintain the restriction between Groups I and II, it is noted that claim 26 is included in both Groups I and II, and therefore, is a linking claim. "If a linking claim is allowed, the examiner must thereafter examine species if the linking claim is generic thereto, or he or she must examine the claims to the non-elected inventions that are linked to the elected invention by such allowed linking claim." MPEP §809.04.

With respect to the election of species requirement, the Examiner is reminded that "upon allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. §1.141." MPEP §809.02(a).

Claims 26-40 and 48-63 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for the use of the phrase "an increased copy number." According to the Examiner, it is unclear what sequence is meant by the phrase.

Applicants respectfully traverse the rejection. "[35 U.S.C.] §112, second paragraph, requires a determination of whether those skilled in the art would understand what is claimed in light of the specification." *Orthokinetics Inc. v. Safety Travel Chairs Inc.*, 1 USPQ2d 1081 (Fed. Cir. 1986). The meaning of the phrase "an increased copy number" in the context of the claim is clear. However, to expedite the prosecution, claim 26 has been amended to recite "an increased copy number of nucleic acid sequences at chromosomal region 20q13.2." Accordingly, withdrawal of the indefiniteness rejection is respectfully requested.

If the examination at the initial stage does not produce a *prima facie* case of unpatentability, then without more, the applicant is entitled to the grant of a patent. *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). For the reasons provided below, unpatentability has not been established.

Claims 26, 56, and 61-63 stand rejected as being anticipated by Morris *et al.* (*Blood* 1991). According to the carryover paragraph of pages 3 and 4 of the Office Action, "Morris *et al.* teach a method for screening cancer, by contacting a nucleic acid sample from a human patient with a probe. Furthermore, the probe taught by Morris *et al.* would inherently hybridize to the claimed SEQ ID NO:9 from 20q13.2 under stringent conditions." Applicants respectfully traverse the rejection.

Morris *et al.* do not anticipate the claims as previously presented or as currently pending. For a prior art reference to anticipate in terms of 35 U.S.C. §102, every element of the claimed invention must be identically shown in a single reference." *In re Bond*, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). Here, the claims are not anticipated, because every element of the rejected claims is not identically shown in Morris *et al.* For example, claim 26 recites "detecting the formation of a hybridization complex to determine the presence or absence of neoplastic cells having an increased copy number of nucleic acid sequences at chromosomal region 20q13.2." However, Morris *et al.* do not teach, *inter alia*, a step of determining increased copy number of

nucleic acid sequences at chromosomal region 20q13.2. Since every element of claim 26 is not taught by Morris *et al.*, the rejection of claims 26, 56, and 61-63 is improper.

Page 4 of the Office Action states that "the probe taught by Morris *et al.* would inherently hybridize to the claimed SEQ ID NO:9 from 20q13.2 under stringent conditions, because the probe taught by Morris et al is 88% similar to the claimed SEQ ID NO:9, under MPSRCH search. Any increase in copy number at 20q13.2 is thus would be inherently detected by said hybridization." In view of these statements, it may be the position of the Examiner that any probe capable of hybridizing to SEQ ID NO:9 from 20q13.2 would satisfy the requirements of the claimed invention.

Applicants respectfully disagree. Since the Office Action does not clearly indicate what portion of the probe taught by Morris *et al.* is 88% similar to SEQ ID NO:9 recited in the claims, it is unclear to Applicants if the probe of Morris *et al.* would inherently hybridize to SEQ ID NO:9 from 20q13.2 under stringent conditions as alleged by the Examiner. Regardless of whether or not the probe can inherently hybridize to SEQ ID NO:9 from 20q13.2, the Examiner is respectfully reminded that the present claims are not directed to a probe, but to a method. Thus, to anticipate the claims, the prior art must not only teach the probe recited in the present claims, but also must teach every element of the claimed method. As described above, Morris *et al.* do not teach every limitation of the claimed method. For example, Morris *et al.* do not teach "detecting the formation of a hybridization complex to determine the presence or absence of neoplastic cells having an increased copy number of nucleic acid sequences at chromosomal region 20q13.2" as recited in the present claims. Morris *et al.* do not even mention chromosome 20, because their work relates to translocation of genes located at chromosome 22 and chromosome 9. Accordingly, the rejection is improper.

Claims 26, 56, and 61-63 were rejected under 35 U.S.C. §102(e) as being anticipated by Stokke *et al.* (U.S. Pat. 5,633,365). According to page 5 of the Office Action, "Stokke *et al.* teach a method for detection of an amplification at about position Flpter 0.825 on human chromosome 20, using probes which are specific to said region (the entire document,

especially table 2). Thus the chromosomal target region taught by Stokke *et al.* is the same as the claimed invention." Applicants respectfully traverse the rejection.

In the instant case, the claims are not anticipated, because every element of the rejected claims is not identically shown in Stokke *et al.* For example, claim 26 recites "detecting the formation of a hybridization complex to determine the presence or absence of neoplastic cells having an amplification or a deletion of nucleic acid sequences at chromosomal region 20q13.2." Stokke *et al.* do not mention, *inter alia*, determining an increased copy number of nucleic acid sequences at chromosomal region 20q13.2. Since every element of the claimed invention is not disclosed in Stokke *et al.*, the rejection is improper.

At page 5 of the Office Action, the Examiner refers to the entire document, especially Table 2 of Stokke *et al.* in rejecting the claims. Applicants respectfully submit that Table 2 of Stokke *et al.* relates to probes for chromosome 17, not to probes for chromosome 20. Therefore, the Examiner's reliance on Table 2 of Stokke *et al.* is misplaced.

It may be the position of the Examiner that the present claims are anticipated, because the probes of Stokke *et al.* broadly encompass the probes recited in the present claims. For example, column 14, lines 23-25 of Stokke *et al.* recite that "the probe binds selectively to a target polynucleotide sequence from about Flpter 0.740 to about Flpter 0.846." Applicants respectfully submit that the claims are not anticipated by Stokke *et al.*, because the regions identified in Stokke *et al.* are, at best, generic to the species identified in the present claims. A genus does not necessarily anticipate a species. *See* MPEP §2131.02. Therefore, chromosomal regions from about Flpter 0.740 to about Flpter 0.846 disclosed in Stokke *et al.* do not anticipate chromosomal region 20q13.2 (*i.e.*, about position FLpter 0.825) recited in the present claims. Therefore, the rejection is improper, and should be withdrawn.

Claims 26-40 and 48-63 were rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not enable any person skilled in the art to use the invention commensurate in scope with these claims. Pages 5-6 of the Office Action state:

> [T]he specification, while being enabled for a method for screening breast cancer, does not reasonably provide enablement for a method for screening any neoplastic cells...[S]creening for neoplastic cells reads on screening for any types of cancer. Yet it is well known in the art, not all types

> of cancer are associated with abnormality of the chromosome 20q13.2...In the absence of sufficient correlation between one example of a method of detecting breast cancer described in the specification, and a method of detecting any type of cancer, and in view of the above contradiction, one of skill in the art would be forced into undue experimentation in order to the use the claimed sequence SEQ ID NO:9 to detect any type of cancer.

Applicants initially note that claim 27 is directed to a method wherein the nucleic acid sample is from a patient with breast cancer, and yet this claim was rejected. As the Examiner acknowledged that the specification enables a method for screening breast cancer, withdrawal of the rejection of claim 27 is respectfully requested.

Applicants respectfully traverse the rejection, because the Office Action fails to establish a *prima facie* case of non-enablement. In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). MPEP §2164.04. Here, the Examiner has not met the initial burden of showing non-enablement of the claimed invention, because the Examiner has not established that undue experimentation would be required to practice the full scope of the claimed method. The Examiner's basis for rejecting the claims appears to be that there is only one working example (*i.e.*, detecting breast cancer) with probes recited in the present claims. However, the Examiner has not made any showing that methods of contacting nucleic acid samples from patients with other cancers or neoplastic cells would be unusually difficult. Furthermore, the Examiner is reminded that "the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without undue amount of experimentation." *In re Borkowski*, 164 USPQ 642, 645 (CCPA 1970). Therefore, the presence of a working example, when in fact none is needed, does not establish a reasonable basis to question the enablement provided for the claimed method. Accordingly, a *prima facie* case of non-enablement is not established, and the rejection should be withdrawn for this reason alone.

Furthermore, Applicants respectfully submit that the claims are fully enabled. Claim 26, as amended, is directed to "a method of detecting the presence or absence of neoplastic cells in a sample having an increased copy number of nucleic acid sequences at chromosome region 20q13.2." The specification clearly provides sufficient information and

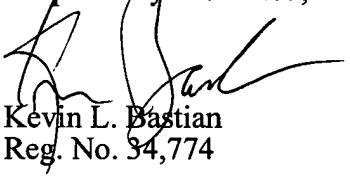
guidance to practice the claimed method. For example, pages 20-22 of the specification disclose probes which are capable of hybridizing to target polynucleotide sequences. The Sequence Listing at pages 55-62 also provides nucleotide sequences of SEQ ID NO:1 through SEQ ID NO:13 recited in the claims. Furthermore, pages 30-31 of the specification, *e.g.*, disclose assays, such as *in situ* hybridization or southern blots, for detecting amplification of nucleic acid sequences in a chromosome. Therefore, in view of this disclosure one skilled in the art can test any biological sample and determine if the sample contains cells having an increased copy number of nucleic acid sequences at chromosome region 20q13.2. Accordingly, the rejection is improper and should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



Kevin L. Bastian
Reg. No. 34,774

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: (415) 576-0200
Fax: (415) 576-0300
KLC
SF 201391 v3

APPENDIX

26. A method of detecting the presence or absence of neoplastic cells in a sample having an increased copy number of nucleic acid sequences at chromosome region 20q13.2, the method comprising:

contacting a nucleic acid sample from a human patient with a probe which hybridizes to a target polynucleotide sequence under stringent conditions that include washing with 0.2x SSC at 65°C for 15 minutes, the target polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, and SEQ ID NO:13 wherein the probe is contacted with the sample under conditions in which the probe hybridizes selectively with the target polynucleotide sequence to form a stable hybridization complex; and

detecting the formation of a hybridization complex to determine the presence or absence of neoplastic cells having an increased copy number of nucleic acid sequences at chromosomal region 20q13.2.

27. The method of claim 26, wherein the nucleic acid sample is from a patient with breast cancer.

28. The method of claim 26, wherein the nucleic acid sample is a metaphase spread or a interphase nucleus.

29. The method of claim 26, wherein the probe comprises a polynucleotide sequence as set forth in SEQ ID NO:1.

30. The method of claim 26, wherein the probe comprises a polynucleotide sequence as set forth in SEQ ID NO:2.

31. The method of claim 26, wherein the probe comprises a polynucleotide sequence as set forth in SEQ ID NO:3.

32. The method of claim 26, wherein the probe comprises a polynucleotide sequence as set forth in SEQ ID NO:4.

33. The method of claim 26, wherein the probe comprises a polynucleotide sequence as set forth in SEQ ID NO:5.

34. The method of claim 26, wherein the probe comprises a polynucleotide sequence as set forth in SEQ ID NO:6.

35. The method of claim 26, wherein the probe comprises a polynucleotide sequence as set forth in SEQ ID NO:7.

36. The method of claim 26, wherein the probe comprises a polynucleotide sequence as set forth in SEQ ID NO:8.

37. The method of claim 26, wherein the probe comprises a polynucleotide sequence as set forth in SEQ ID NO:9.

38. The method of claim 26, wherein the probe comprises a polynucleotide sequence as set forth in SEQ ID NO:10.

39. The method of claim 26, wherein the probe comprises a polynucleotide sequence as set forth in SEQ ID NO:12.

40. The method of claim 26, wherein the probe comprises a polynucleotide sequence as set forth in SEQ ID NO:45.

48. The method of claim 26, wherein the probe comprises a polynucleotide sequence that hybridizes to SEQ ID NO:1 under stringent conditions that include washing with 0.2x SSC at 65°C for 15 minutes.

49. The method of claim 26, wherein the probe comprises a polynucleotide sequence that hybridizes to SEQ ID NO:2 under stringent conditions that include washing with 0.2x SSC at 65°C for 15 minutes.

50. The method of claim 26, wherein the probe comprises a polynucleotide sequence that hybridizes to SEQ ID NO:3 under stringent conditions that include washing with 0.2x SSC at 65°C for 15 minutes.

51. The method of claim 26, wherein the probe comprises a polynucleotide sequence that hybridizes to SEQ ID NO:4 under stringent conditions that include washing with 0.2x SSC at 65°C for 15 minutes.

52. The method of claim 26, wherein the probe comprises a polynucleotide sequence that hybridizes to SEQ ID NO:5 under stringent conditions that include washing with 0.2x SSC at 65°C for 15 minutes.

53. The method of claim 26, wherein the probe comprises a polynucleotide sequence that hybridizes to SEQ ID NO:6 under stringent conditions that include washing with 0.2x SSC at 65°C for 15 minutes.

54. The method of claim 26, wherein the probe comprises a polynucleotide sequence that hybridizes to SEQ ID NO:7 under stringent conditions that include washing with 0.2x SSC at 65°C for 15 minutes.

55. The method of claim 26, wherein the probe comprises a polynucleotide sequence that hybridizes to SEQ ID NO:8 under stringent conditions that include washing with 0.2x SSC at 65°C for 15 minutes.

56. The method of claim 26, wherein the probe comprises a polynucleotide sequence that hybridizes to SEQ ID NO:9 under stringent conditions that include washing with 0.2x SSC at 65°C for 15 minutes.

57. The method of claim 26, wherein the probe comprises a polynucleotide sequence that hybridizes to SEQ ID NO:10 under stringent conditions that include washing with 0.2x SSC at 65°C for 15 minutes.

58. The method of claim 26, wherein the probe comprises a polynucleotide sequence that hybridizes to SEQ ID NO:11 under stringent conditions that include washing with 0.2x SSC at 65°C for 15 minutes.

59. The method of claim 26, wherein the probe comprises a polynucleotide sequence that hybridizes to SEQ ID NO:12 under stringent conditions that include washing with 0.2x SSC at 65°C for 15 minutes.

60. The method of claim 26, wherein the probe comprises a polynucleotide sequence that hybridizes to SEQ ID NO:45 under stringent conditions that include washing with 0.2x SSC at 65°C for 15 minutes.

61. The method of claim 26, wherein the probe is labeled.

62. The method of claim 61, wherein the label is a fluorescent label.

63. The method of claim 26, wherein the nucleic acid sample is a chromosome sample.